REMARKS

Claims 1, 2, 4, 6, 10-11, 15, 17, 19, 23, 26, 28, 30, 34, 53, 57, and 69 are amended herein. Support for the amendment of claims 1, 2, 4, and 6 can be found in the specification at page 19, lines 3-7. Support for the amendment of claims 10, 53, and 57 can be found in the specification at page 10, lines 19-28. Support for the amendment of claims 11, 15, 17, 19, 23, 26, 28, and 30 can be found in the specification at page 29, line 25 through page 30, line 10. Claims 34, 66, and 67 were amended to correct form. Support for the amendment of claim 69 can be found in the specification at page 10, lines 32-33 and page 17, lines 29-30.

Claims 3, 5, 7-9, 14, 16, 18, 20, 25, 27, 29, 31-33, 36-37, 39, and 42-47 were previously canceled. Following entry of this amendment, claims 1-2, 4, 6, 10-13, 15, 17, 19, 21-24, 26, 28, 30, 34, 38, 40-42, and 48-69 are pending.

No new matter is added by any of the foregoing amendments. Reconsideration of the subject application is respectfully requested.

Telephone Interview

Applicants thank Examiner Helms for the helpful telephone conference on August 8, 2003 with Applicants' representative, Anne Carlson, Ph.D.

Formalities from Office Action

Applicants acknowledge that the election of Group 1 (claims 1-35, 38-41) is made final.

Rejections Under 35 U.S.C. §112, second paragraph

Claims 10, 34-35, 53 57 58, and 69 are rejected under 35 U.S.C. 112, second paragraph as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

a) Claims 10, 53 and 57

Claims 10, 53 and 57 are rejected as allegedly being unclear as to whether "three light chain hypervariable regions" and "three heavy chain hypervariable regions" refers to CDRs or to

other residues, including the framework residues. Applicants respectfully disagree with this rejection. The specification clearly states at page 10, lines 19-23 that the hypervariable regions are CDRs and nonhypervariable regions are framework regions. Thus, it would be definite and clear to one of skill in the art that the hypervariable region refers to the CDRs. However, solely to advance prosecution in this application, Applicants amend claims 10, 53, and 57 to recite that "the parental humanized antibody comprises three L-CDRs and three H-CDRs of the murine monoclonal CC49 antibody." Reconsideration and withdrawal of the rejection are respectfully requested.

b) Claims 34 and 35

Claims 34 and 35 are rejected as allegedly being indefinite for not being clear if both (1) a threonine at position 94 in L-CDR3 and (2) a serine at position 97 in L-CDR3 are required in the humanized anti-TAG-72 CC49 antibody because if so, (3) a threonine at position 94 and a serine at position 97 does not add anything further to the claim. Applicants respectfully disagree and note that claim 34 recites limitations (1), (2), and (3) in the alternative. Thus, the humanized anti-TAG-72 CC49 antibody can have either a threonine at position 94, a serine at position 97 or both. However, in order to advance prosecution in this case, Applicants amend claim 34 to recite "wherein (1) a threonine is at position 94 in the L-CDR3, or (2) a serine. . ." to more clearly define Applicants' invention. Claim 35 recites only a specific embodiment of claim 34, notably that threonine is at position 94. Thus, claim 35 is clearly further limiting of claim 34. Applicants submit that this amendment of claim 34 removes the rejection. Reconsideration and withdrawal of the rejection are respectfully requested.

c) Claim 58

Claim 58 is rejected as allegedly being indefinite because the residues recited in the claim are those that would be at positions in the 21/28'CL antibody. Claim 58 depends from claim 24. Claim 24 recites that the humanized anti-TAG-72 CC49 antibody has at least one amino acid at positions 60, 61, 62, or 64 in the murine H-CDR2 that is replaced with an amino acid at a corresponding position from human monoclonal 21/28'CL H-CDR2. Claim 58 recites that the corresponding positions are the *human* amino acids at positions 12, 13, 14, or 16, as set forth in SEQ ID NO: 11. These corresponding amino acids replace *murine* amino acids at positions 60,

61, 62 or 64. The Examiner is correct in interpreting that the numbers recited in claim 58 refer to positions in the 21/28'CL antibody (SEQ ID NO: 11). Thus, based on the above discussion, claim 58 is definite. Reconsideration and withdrawal of the rejection are respectfully requested.

d) Claim 69

Claim 69 is rejected as allegedly being indefinite for the term "use," because it is allegedly unclear what use is intended. Applicants respectfully disagree with this assertion. However, solely to advance prosecution of this application, Applicants have amended claim 69 to recite that the kit comprises "instructions for using the humanized antibody to treat or detect a cancer cell expressing TAG-72." Applicants submit that this amendment removes the rejection. Reconsideration and withdrawal of the rejection are respectfully requested.

Rejections Under 35 U.S.C. §112, first paragraph

a) Claims 1-2, 4, 6, 10-13, 15, 17, 19, 21-24, 26, 28, 30, 38, 40-41, 48-49, 51-55, 57-64, and 66-69

Claims 1-2, 4, 6, 10-13, 15, 17, 19, 21-24, 26, 28, 30, 38, 40-41, 48-49, 51-55, 57-64, and 66-69 are rejected because allegedly the specification, while enabling for a humanized antibody comprising L-CDR1 and L-CDR2 of LEN "does not reasonably provide enablement for a humanized antibody wherein CDR1 or 2 of the light chain are from any antibody or from any CDR in the LEN antibody." Applicants respectfully disagree with this rejection. However, solely to advance prosecution, claims 1, 2, 4 and 6 are amended herein to recite that L-CDR1 and L-CDR2 are human monoclonal LEN antibody L-CDR1 and L-CDR2. Claims 11, 15, 17, 19, 23, 26, 28, and 30 are amended to recite that L-CDR3, H-CDR1, H-CDR2, and H-CDR3 are murine CC49 monoclonal antibody L-CDR3, H-CDR1, H-CDR2, and H-CDR3. In addition, claims 11, 15, 17, 19, 23, 26, 28, and 30 are amended to recite that L-CDR1 and L-CDR2 are either murine CC49 or human LEN L-CDR1 and L-CDR2. Finally, claims 66 and 67 are amended to recite "L-CDR3 from the murine CC49 antibody."

Applicants submit that the amendment of the claims 1, 2, 4, 6, 11, 15, 17, 19, 23, 26, 28, and 30 to refer to CDRs from a specific antibody removes the rejection. Claims 10, 38, 40-41,

48-49, and 69 depend, directly or indirectly, from claim 1. Claims 12, 13, 21, 22, 51-55, and 68 depend, directly or indirectly, from claim 11. Claims 24 and 57-64 depend, directly or indirectly, from claim 23. Reconsideration and withdrawal of the rejection are respectfully requested.

b) Claims 1-2, 4, 6, 10-13, 15, 17, 19, 21-24, 26, 28, 30, 34-35, 38, 40-41, and 48-69

Claims 1-2, 4, 6, 10-13, 15, 17, 19, 21-24, 26, 28, 30, 34-35, 38, 40-41, and 48-69 are rejected because allegedly "the specification does not provide evidence that the claimed biological materials are (1) known and readily available to the public; (2) reproducible from the written description." Specifically, the Office action alleges that it is not clear if humanized CC49 (parental HuCC49) is available. Applicants respectfully disagree with this rejection.

The parental humanized HuCC49 antibody is fully described in U.S. Patent Number 6,495,137 and its sequence is provided in this U.S. patent. Moreover, HuCC49 is expressed by a cell line deposited as ATCC HB-12404. We have been informed by Marie Harris of the ATCC Patent Department that ATCC HB-12404 is indeed the humanized monoclonal CC49 antibody and that all restrictions for this deposit have been released. Thus, the parental humanized CC49 antibody is both (1) known and readily available to the public, and (2) reproducible from the written description in U.S. Patent Number 6,495,137. Reconsideration and withdrawal of the rejection are respectfully requested.

Rejections Under 35 U.S.C. §103

Claims 1-2, 4, 6, 10-13, 15, 17, 19, 21-24, 26, 28, 30, 34, 38, 40-41, and 48-69 are rejected as allegedly being obvious over Mezes *et al.*, (U.S. Patent Number 6,495,137, hereinafter the '137 patent, filed October 30, 1997), in light of Padlan *et al.*, (FASEB J. 9:133-139, 1995), as evidenced by Tamura *et al.* (*J. Immunol.*, 164:1432-41, 2000). Applicants respectfully disagree with this assertion.

The '137 patent teaches that an antibody can be humanized by combining murine CC49 CDRs with human light chain (LEN) and heavy chain (21/28'CL) framework regions. The Office action acknowledges that the '137 patent does not teach an antibody with L-CDR1 and L-CDR2 from LEN, but maintains that it would have been *prima facie* obvious to one of ordinary

skill in the art to replace CC49 L-CDR1 and L-CDR2 with LEN L-CDR1 and L-CDR2 because it "would obviously result in a less immunogenic antibody compared to the HUCC49 parent" (Office action at page 11, lines 14-15).

Applicants' specification teaches that, unexpectedly, only the replacement of specific CC49 CDRs with their corresponding LEN or 21/28'CL CDR resulted in a reduction in immunogenicity. For example, the replacement of CC49 L-CDR1 or L-CDR2, or both, with the corresponding CDR from LEN resulted in a slight reduction in immunogenicity compared to the parental HuCC49. However, the replacement of CC49 H-CDR1 or H-CDR3 with the corresponding CDR from LEN did not show any measurable change in immunogenicity compared to the parental HuCC49 (see the specification at page 12, lines 12-22). Thus, HuCC49 variants with an LEN L-CDR1 and/or L-CDR2 demonstrate an unexpectedly superior result, compared to HuCC49 variants that have an LEN H-CDR1 or H-CDR3. Applicants' specification teaches that the introduction of human CDRs does not *necessarily* result in a reduction in immunogenicity. Thus, it is only Applicants' work that identifies exactly which human CDRs yield a HuCC49 variant with reduced immunogenicity.

Padlan *et al.* teaches that the substitution of specificity determining regions (SDRs) can produce humanized antibodies with preserved reactivity and reduced immunogenicity. The positions of proposed SDRs are also disclosed in Padlan *et al.* The Office action states that it would have been *prima facie* obvious to one of ordinary skill in the art "to have used residues identified in Padlan *et al.* as important for antigen binding and replace the residues that are not important with human residues for reduced immunogenicity in the humanized antibody of Mezes *et al.*" (italics added; Office action at page 10, lines 20-22).

The legal standard applicable to determinations of obviousness based on a combination of references was reiterated by the Court of Appeals for the Federal Circuit in *In re Dow Chemical Co.*, 837 F.2d 469, 473, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988):

> The consistent criterion for the determination of obviousness is whether the prior art would have suggested to one of ordinary skill in the art that this process should be carried out and would have a reasonable likelihood of success, viewed in the

> light of the prior art [citations omitted]. **Both the suggestion and the expectation of success must be founded in the prior art, not in the applicant's disclosure** [emphasis added].

Therefore, three elements must be established in order to make a *prima facie* case of obviousness. First, the prior art must suggest, or provide the incentive for, the combination of references. Second, the combination as suggested or motivated by the art must yield the process or invention claimed. Third, the prior art must provide a reasonable expectation of success of the claimed process. At no point may the applicant's disclosure be used to satisfy the three elements. If any of these elements is absent, the rejection based on obviousness is unsupported.

Neither the '137 patent, nor Padlan *et al.*, suggests the **specific amino acids** to be substituted with the murine CC49 CDRs. The '137 patent does not teach or suggest the substitution of murine CDR residues. The '137 patent only teaches the inclusion of murine CC49 CDRs within human LEN or 21/28'CL frameworks. Although Padlan *et al.* suggests substituting murine CDR residues with other amino acids, there is no specific teaching to substitute CC49 CDR residues with any specific amino acids, let alone with a residue from an LEN or a 21/28'CL CDR. In the absence of such a teaching, Padlan *et al.* does not establish a *prima facie* case of obviousness.

Moreover, Padlan *et al.* is only an "invitation-to-try", which is not an appropriate standard of obviousness, as held by the Court of Appeals for the Federal Circuit *In re O'Farrell*, 853 F.2d 894, 903-904, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988). For example, the court in *O'Farrell* stated:

> In others, what was "obvious-to-try" was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it.

In fact, Padlan *et al.* acknowledges that "SDRs are probably unique to each antibody and their identification may only be possible with the determination of the three-dimensional structure of the complex with antigen" (Padlan *et al.*, page 138, right column, lines 7-9). MPEP

§2141.02 states that "[a] prior art reference must be considered in its entirety." Thus, although Padlan *et al.* suggests that certain positions correspond to residues that may or may not be involved in antigen binding, Padlan *et al.*, also recognizes that this is merely an invitation to try and that these positions may differ with each antibody.

Although it may have been "obvious-to-try" substituting specific residues in light of Padlan *et al.*, it is only the work of the Applicants that identifies exactly which residues are involved in antigen binding. For example, Padlan *et al.* suggests that residue 97 in L-CDR3 and residues 60, 61, 62, and 64 in H-CDR2 are not SDRs, thus their substitution should not affect antigen binding. The substitution of residue 97 in L-CDR3 (variant ^{97}L) and the substitution of residues 60, 61, 62, and 64 in H-CDR2 (variant $^{60\text{-}62,64}$H) resulted in relative binding affinities (Ka) that were comparable to the parental HuCC49 (specification at page 34, lines 10-12). However, surprisingly, the combination of all four amino acid substitutions resulted in a variant (^{97}L /$^{60\text{-}62,64}$H) with a relative binding affinity that was almost twice that of parental HuCC49 (specification at page 34, lines 20-21). Thus, HuCC49 variant ^{97}L/$^{60\text{-}62,64}$H (claims 13 and 24) demonstrates an unexpected superior binding affinity compared to variants ^{97}L and $^{60\text{-}62,64}$H. It is only the work of the Applicants, and not the teachings of the '137 patent or Padlan *et al.*, that demonstrates that the combination of residues 97 in L-CDR3 and 60-62, 64 in H-CDR2 is clearly involved in antigen binding.

Tamura *et al.* is the inventors' own work and was published after the filing date of the subject application. Tamura *et al.* simply states what was already known: humanization of murine antibodies, by grafting all of the CDRs of a murine antibody onto a human antibody framework, can reduce the human anti-murine antibody (HAMA) response in patients, but the retention of murine CDRs could still evoke an anti-variable region response. Padlan *et al.* suggests which amino acid *positions* are involved in antigen binding. Tamura *et al.* only confirms that Padlan *et al.* was a mere invitation to experiment. It is the work of the Tamura *et al.* that shows the replacement of murine amino acid residues with specific amino acids (see Tamura *et al.*, page 1433, right column, lines 6-9). This is the inventors' own work, which was published after the filing date of the present application. Tamura *et al.* does not, in any way,

indicate that the prior art makes it obvious which specific amino acid should be used to replace a particular murine residue.

Consequently, Applicants submit that neither the '137 patent, Padlan *et al.*, nor Tamura *et al.*, alone or in combination, renders obvious pending claims 1-2, 4, 6, 10-13, 15, 17, 19, 21-24, 26, 28, 30, 34, 38, 40-41, and 48-69. Reconsideration and withdrawal of the rejection is respectfully requested.

Claim 69 is rejected as allegedly being obvious over Mezes *et al.*, (U.S. Patent Number 6,495,137, hereinafter the '137 patent, filed October 30, 1997), in light of Padlan *et al.*, (FASEB J. 9:133-139, 1995), as evidenced by Tamura *et al.* (*J. Immunol.*, 164:1432-41, 2000). Applicants respectfully disagree with this assertion. As discussed above, the antibody of claim 1 is not obvious over the '137 patent, Padlan *et al.*, nor Tamura *et al.*, alone or in combination. As claim 69 depends from claim 1 and incorporates all of the limitations thereof, claim 69 is not obvious. Reconsideration and withdrawal of the rejection is respectfully requested.

CONCLUSIONS

Based on the foregoing, the claims are in condition for allowance and notification to this effect is requested. If for any reason the Examiner believes that a telephone conference would expedite allowance of the claims, please telephone Applicants' undersigned representative at (503) 226-7391.

Respectfully submitted,

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